Remarks

Amendments to the Claims

Claim 26 has been amended to define antibodies which are reactive with only a single subunit of the Shiga like toxin II. Support for this amendment is found in the application at page 7, lines 12-15. Support is also found in pending claim 30, which the examiner has previously examined, and therefore does not raise new issues. Claim 33 has been amended to define antibodies reactive with the beta subunit.

Claim 26 has also been amended to clarify that the source of the shiga like toxin II is *E. coli* which causes hemolytic uremic syndrome in humans. Although it is believed this was implicit in the claims as previously pending, it has now been made explicit. Support is found in the application is found at page 7, lines 5-9.

Entry of these amendments should facilitate allowance or narrow issues on appeal, and do not raise new issues since the change in claim scope is based on a claim currently pending in dependent form and previously examined on the merits.

The application demonstrates the efficacy of antibodies immunoreactive with a single subunit in preventing HUS associated mortality. Figure 5 demonstrates that applicants' antibodies are neutralizing antibodies. Figure 6 shows the average survival time of mice exposed to sbiga like toxin II ("Stx2"), without treatment, and after treatment with antibodies to subunit A (, subunit B, or a combination thereof. Table 5 on page 59 shows the specificity of the anti-Stx 2 antibodies. Attached with this Response is a copy of Sheoran, et al., "Tsx2-specific human monoclonal antibodies protect mice against lethal infection with *E. coli* expressing Stx2

variants" Infect. Innum. 71(6):3125-3130 (June 2003). This provides further evidence that the monoclonal antibodies to the individual subunits are protective, but that their activities are different depending on the specificity. As the paper demonstrates, the anti-Stx2 A antibodies have broader protectivity than the anti-Stx2 B antibodies.

Rejection Under 35 U.S.C. § 103

Claims 26-36 were again rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,512,282 to Krivan *et al.* ("Krivan") and Perera *et al.* J. Clin. Microbiol. 26(10):2127-2131 (1988) ("Perera") in view of WO 90/07861 by Protein Design Labs, Inc ("Queen"). and Engelman *et al.* "Human Hybridomas and Monoclonal Antibodies ed. Engleman, Foung, Larrick, Raubitschek (Plenum Press 1985) pp. 95-112 ("Engelman"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

As discussed above, the claims have been narrowed to define only the antibodies that are specific for a particular subunit. Other important limitations are that the antibodies are neutralizing antibodies and are immunoreactive with the organism causing disease in humans.

None of the prior art discloses the use of an antibody to only a single subunit of the Stx2 for treatment or prevention of disease. None of the prior art recognizes that one only has to block Stx2 to prevent the mortality and other extremely serious complications of HUS associated with certain highly virulent strains of *E. coli*. None of the prior art recognizes that the toxins associated with strains of *E. coli* that infect humans, as compared to other animals, are different, and that antibodies to toxin from animal strains may not be effective in treating or preventing

complications of HUS. None of the prior art recognizes that one can block only a single subunit and still treat or prevent the high mortality or serious complications of HUS.

As discussed in more detail below, the art recognizes that antibodies should be useful in the treatment of HUS (Krivan). The art recognizes that one can make antibodies to just one subunit (Perera) which are useful in diagnostics. There is nothing that would lead one to substitute these subunit specific antibodies into Krivan, determine an effective dosage, and then have a reasonable expectation of success. None of the art demonstrates any successful treatment or prevention of clinical symptoms.

Therefore one skilled in the art would not be lead either to select antibodies as defined by all claims now pending, not just claim 30 as previously presented, nor to have a reasonable expectation of success if one did so.

The Prior Art:

Krivan

Krivan teaches polyclonal, monospecific bovine antibodies for the detection of a Shiga-like toxin or for treating hemolytic uremic syndrome. There is no disclosure or suggestion in this reference to obtain a human monoclonal antibody that will bind to, and specifically neutralize, a Shiga-like toxin II in humans. Moreover, as discussed in Dr. Tzipori's declaration, previously submitted, Krivan only teaches oral administration of antibody which would not be effective in treating or preventing human disease due to digestion of the antibody in the human stomach prior to reaching the intestines.

In fact, Krivan says his antibodies and invention ***are not, and cannot be, useful in humans.*** As the following excerpt from the patent makes clear, the animals to be treated to make antibodies ***do not possess receptors for the toxin (thereby excluding humans), and the resulting antibodies therefore would not be administerable to humans (it is well known one cannot administer bovine antibodies to humans):***

"To achieve the objects and accordance with the purpose of the invention, as embodied and broadly described herein, the present invention provides an antitoxin to one or more SLTs. It comprises purified IgG that contains high titer, monospecific polyclonal antibodies to a Shiga-like toxin. (col. 6, lines 17-21)

The antibodies can be purified from the IgG. Therefore, the invention also provides high titer, monospecific, purified polyclonal antibodies to an SLT. Preferably, the antibodies comprise bovine IgG." (col. 6, lines 22-26)

"As used herein, the term "Shiga-like toxin (SLT)" refers to any cytotoxin similar in both structure and function to Shiga toxin. Known SLTs include SLT-I, SLT-II, and SLT-III. They also include known variants of SLT-II, which are SLT-IIv, SLT-IIvh, and SLT-IIvp. The term encompasses the presently unknown SLTs or variants thereof that may be discovered in the future, since their characterization as an SLT or variant thereof will be readily determinable by persons skilled in the art." (col. 7, line 65 to col. 8, line 6)

"The purified IgG of the invention is made by a novel modification of standard techniques for making polyclonal antibodies by inoculating an animal with an antigen and recovering immunoglobulins from a fluid, such as serum, that contains the immunoglobulins

after the animal has had an immune response. The inventors surprisingly and unexpectedly discovered that they were able to inoculate a bovine animal with a purified, preferably active, SLT without significant ill effect to the animal." (page 8, lines 7-15)

"Without wishing to be bound by theory, the inventors hypothesized that the cell membranes of the cells of such an animal do not contain a receptor for SLTs or only contain low levels of receptors, when compared to other mammals or humans. Presumably, this allows high amounts of purified, active toxin to be inoculated into the animal and presumably allows the toxin to remain in unbound form longer in the animal, thereby creating a much greater antigenic response." (col. 8, lines 16-24)

"***Therefore, the method of the invention is applied to any animal that has few or no receptors to SLTs. Such animals can be identified by those skilled in the art through standard techniques involving the injection of an SLT into the animal and the observation of its effect on the animal and the titer of antibodies produced by the animal.*** " (emphasis added) (col. 8, lines 25-30)

Accordingly, there is no teaching in Kriven of the need to make human or humanized antibodies to SLT-II, no teaching of how to make such antibodies, no recognition that this is the critical toxin to protect against, much less what an effective dosage is, and even less so that one might target a specific subunit of the toxin. Polyclonal antibodies would not be specific to a single subunit ***unless one actively took the step of removing antibodies from the mixture which are reactive with the other subunit and the combination of subunits.*** One skilled in the art

would be led away from what applicants' have, from the teaching of Krivan which is to use bovine antibody reactive with multiple epitopes in the toxin, which is administered parenterally.

Perera

Perera is relied upon for its teaching of toxin neutralization. Perera teaches five monoclonal antibodies which bind to the α-subunit of SLT-II and were able to neutralize the toxin as assayed using HeLa cells or Vero cells *in vitro* (for example, see Materials and Methods, page 2128, 2nd column). As noted at page 2130, col. 2, the antibodies are useful in diagnostics of disease. There is no mention of therapy other than to note that the shiga like toxins may play a role in disease "although no direct proof for the involvement of SLTs in pathogenesis has yet been demonstrated." Perhaps more importantly, page 2131, col. 1, discusses the relative specificity and sensitivity of the antibodies; and notes that none of the antibodies to the Stx2 only were able to detect organisms; antibodies to Stx2 which were effective were only able to detect organisms producing both Stx1 and Stx2. Accordingly, one would not be led by Perera to use these antibodies in therapy, nor one would have a reasonable expectation of success using just an antibody to Stx2, much less to a single subunit of St2. The diagnostic results here clearly teach away from the use of the anti-Stx2 antibodies.

Perera even in combination with Krivan does not teach that these monoclonal antibodies alone would be effective in treating or preventing HUS, nor in what amount. There is not only no teaching of a therapeutic use, there is nothing that would lead one to estimate a dosage.

The following references were cited merely to show that humanized and/or recombinant antibodies could be made.

Queen

Queen generalizes as to the advantages of humanized antibodies over non-human antibodies. It should be noted that the advantages described therein, are generally directed to combinations of humanized light and heavy chains with donor immunoglobulin CDRs. These combinations are produced using recombinant genetic and biochemical techniques. The techniques do not incorporate the use of an intact "immune system" to produce such humanized monoclonal antibodies.

Engelman

Engelman is also relied upon for teaching advantages of humanized antibodies over non-human antibodies.

The Legal Standard

"References relied upon to support a rejection under 35 USC 103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public." *Application of Payne*, 606 F.2d 303, 314, 203 U.S.P.Q. 245 (C.C.P.A. 1979); *see Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 13 U.S.P.Q.2d 1301 (Fed. Cir. 1989). A publication that is insufficient as a matter of law to constitute an enabling reference may still be relied upon, but only for what it discloses. *See Reading & Bates Constr. Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 651-652, 223 U.S.P.Q. 1168 (Fed. Cir. 1984); *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569 (Fed. Cir. 1991).

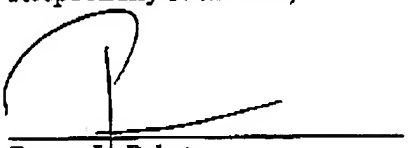
Krivan does not place one of skill in the art with antibodies to SLT-II which would be effective to treat or prevent HUS. Krivan only provides animal antibodies, and it is not clear to

what toxin - it appears that it is only to the SLT forms that cause animal disease, not to the SLT-II form causing HUS. Perera does not teach antibodies for therapeutic use and suggests that antibodies to subunits of Stx2 are not as effective as antibodies to Stx1.

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *See In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication. Here, the references do not teach one skilled in the art to select an antibody to a subunit of Stx2, in a therapeutically effective dosage, to treat or prevent HUS.

Allowance of claims 26-36, as amended, is respectfully solicited.

Respectfully submitted,



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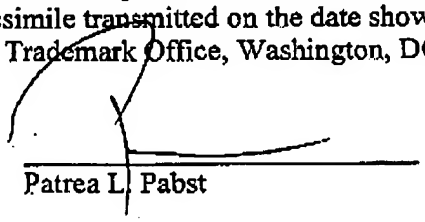

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